REMARKS

Claims 1, 4-15 and 17-47, as amended, and new claims 48-49 appear in this application for the Examiner's review and consideration. Claims 2, 3 and 16 are canceled without prejudice. Claims 32 and 38 have been currently amended to correct a typographical error and have been withdrawn as directed to non-elected subject matter. New claims 48 and 49 have been added. As no new matter is introduced, entry of the amendments and new claims at this time is respectfully requested.

In response to the Examiner's restriction requirement among Groups I-XXX (amino acid molecules, claims 4-10, 15-22 and 31), Groups XXXI-LII (nucleic acid molecules, claims 11-14 and 23-30), Group LIII (method of treatment, claims 32-37), Group LIV (method of treatment, claims 38-43) and Groups LV-LXXXIV (method of screening, claims 45-47), Applicants elect, with traverse, Group I-XXX which includes product claims 4-10, 15-22 and 31.

In addition, Applicants were requested to further restrict and select a particular protein tyrosine kinase receptor. Applicants select group XVI, directed to FGFR3.

Applicants were requested to elect amino acid sequences for examination. Applicants elect group "ac" directed to the set SEQ ID NO:113 and SEQ ID NO:102 for the V_H and V_L; and group "bc" for V_H-CDR3 and V_L-CDR3.

The Applicants respectfully traverse the restriction requirement for the following reasons. Despite decades of attempts to generate neutralizing antibodies to receptor protein tyrosine kinases (RPTK) and FGFRs in particular, prior to the filing of the present application there were no prior art neutralizing antibodies to constitutively active receptor protein tyrosine kinases. Constitutively activated RPTK are involved in a multitude of pathological conditions and there exists a genuine need for molecules able to block their activity. For example, constitutively activated FGFRs cause skeletal dysplasias, craniosynostosis disorders and certain cancers (discussed in present application); constitutively activating mutations of c-kit receptor tyrosine kinase confer ligand-independent growth and tumorigenicity of ligand-dependent hematopoietic cell lines (Kitayama, H. et al., 1995. Blood 85(3):790-798); ligand independent activation of Met activity in cells is thought to be a key event underlying tumor metastasis (Danilkovitch-

Miagkova and Zbar. 2002. J Clin Invest, 109(7):863-867). There are numerous examples in the scientific literature.

RPTKs are unified by several features, including an extracellular ligand binding domain, a transmembrane domain and an intracellular tyrosine kinase domain. The RPTKs are further activated by dimerization and ligand binding to the dimerized form. In fact, the structure and function of RPTKs are highly conserved throughout evolution from nematodes (*C. elegans*), insects (*Drosophila*), and mammals including humans. Although the ligands may be different the downstream elements activated by this superfamily of receptors is highly conserved. Similarly, the FGFRs belong to a subclass of the RPTK superfamily and share many additional structural features including an acidic region between the first and second Ig loops and an intracellular split tyrosine-kinase domain.

The difficulty in raising neutralizing antibodies to active RPTK *in vivo* lies in part in the requirement that they must recognize a dimeric or multimeric structure rather than a monomeric or linear sequence and in part due to the highly conserved sequences between the human and other mammalian sequences. The present inventors developed a method for *ex vivo* screening using soluble functionally intact high affinity dimeric forms of FGFR to overcome these difficulties.

Additionally, there were no prior art human antibodies that block activation of the FGF receptors. The difficulty in generating antibodies to FGFR is largely due to the almost full sequence homology between human and other mammalian species FGFRs. The difficulty was emphasized in a recent manuscript published by Amgen (Wei, P. et al. 2006. Hybridoma 28(3):115-124) wherein the authors generated monoclonal antibodies to human KGFR, a member of the FGFR family of RPTK in a unique immunocompromised mouse strain. The authors state "[a]ntibodies specific against KGFR have been difficult to generate largely due to the high homology between FGFR2c and between human and mouse KGFR (>98%)." (pg 115, 2nd col., last paragraph).

Therefore, the present application provided a significant advancement in the field of antibody research and therapy by providing neutralizing antibodies to constitutively activated and to ligand-dependent FGFRs; and a novel screening method.

The Examiner states on page 8 of the Office communication that the claims are drawn to multiple amino acid sequences, which are considered to be unrelated, since each sequence claimed is structurally and functionally independent and distinct due to their unique amino acid sequence. The antibodies disclosed in the present application are functionally unified in that they all inhibit activation of FGFR.

The V_H-CDR3 and the V_L-CDR3 sequences are all short peptides (8-18 amino acids) and would not pose undue burden on the Patent and Trademark Office to search. Furthermore, the V_H-CDR3 and the V_L-CDR3 sequences disclosed in SEQ ID NOS:8-29 are essentially the same sequences as those disclosed in V_H and V_L sequences of SEQ ID NOS:92-113 with only slight sequence differences in the framework domains.

In view of the following, it is respectfully submitted that at least claims 1, 4-10, 15, 18-22, 31, and 48-49 should be examined at this time. Furthermore, it is understood that method claims 32-47 should be rejoined with the other claims when claim 1 is found to be allowable.

In addition, it is respectfully submitted that the current claims are patentable. Accordingly, the entire application is believed to be in condition for allowance, early notice of which would be appreciated.

Respectfully submitted,

Date: 12/4/06

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